UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/782,650	02/12/2001	Arnold J. Levine	20553D000611	7053

20350 7590 01/17/2003

TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

EXAMINER	
SHUKLA, RAM R	

ART UNIT	PAPER NUMBER
1632	18

DATE MAILED: 01/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

file

Office Action Summary	Application No. 09/782,650	Applicant(s) LEVINE ET AL.	
	Examiner Ram R. Shukla	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,28 and 29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,28 and 29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Applicant's election without traverse of the invention of group I, claims 1-7 and 28-29 in Paper No. 14 is acknowledged.

2. Claims 15-27 have been cancelled.

3. Claims 1-7 and 28-29 are instantly under consideration.

4. Regarding the amendment filed 10-09-01 (paper #8), it is noted that page 2 of the amendment was missing and therefore, the amendment has not been entered entirely. Applicants were contacted to provide a copy of the missing page of the amendment, which they faxed on 1-8-03.

5. **Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.**

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Specifically the application fails to comply with CFR 1.821(d), which states:

> (d) Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing " in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO: " in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

For example, the specification discloses nucleotide sequences on page 48 (line 32) and page 49 (line 1). However, these sequences are not identified by sequence identifiers.

For compliance with sequence rules, it is necessary to include the sequence in the "Sequence Listing" and identify them with SEQ ID NO. In general, any sequence that is disclosed and/or claimed as a sequence, i.e., as a string of particular bases or amino acids, and that otherwise meets the criteria of 37 CFR

1.821(a), must be set forth in the "Sequence Listing." (see MPEP 2422.03). Applicants are required to review the entire specification for any nucleotide sequences or amino acid sequences and include the sequences in sequence listing.

For the response to this office action to be complete, Applicants are required to comply with the Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Information Disclosure Statement

6. The information disclosure statement filed 10-09-01 fails to comply with 37 CFR 1.98(a)(1), which requires a list of all patents, publications, or other information submitted for consideration by the Office. It has been placed in the application file, but the information referred to therein has not been considered.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-7 and 28-29 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is referred to the revised interim guidelines on written description published January 5, 2001 in the Federal Register, Volume 66, Number 5, page 1099-111 (also available at www.uspto.gov).

Claimed invention is directed to a chimeric molecule comprising an angiogenic factor linked to a targeting molecule that specifically binds to a vascular endothelium and a pharmaceutical composition comprising the molecule. However,

the specification does not provide sufficient written description support for the claimed molecules as discussed below.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. When the claims are analyzed in light of the specification, instant invention recites a genus, a chimeric molecule that comprises an angiogenic factor and a targeting molecule. However, the specification does not teach what is the complete structure of representative species of the genus. Except for disclosing that peptides are linked to VEGF and that the chimeric molecule is a fusion protein, the specification does not describe the structure of a representative number of species of the genus.

Next, then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e. other than nucleotide sequence), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, the only identifying characteristic is that the chimeric molecule is specifically targeted to a vascular endothelium, however, the specification does not describe as to what is identifying characteristics among different species of the genus.

Accordingly, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that the applicant is in possession of the broad genus of the modulators or agents at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genus.

9. Claims 1-7 and 28-29 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed

invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

Claimed invention is directed to a chimeric molecule comprising an angiogenic factor linked to a targeting molecule that specifically binds to a vascular endothelium and a pharmaceutical composition comprising the molecule. It is noted that the only intended use for the claimed chimeric molecules is for treatment and as a pharmaceutical composition. Accordingly, the enablement of the claimed composition is considered for treatment. It is noted that the specification does not provide any guidance for treating any disease using the claimed chimeric molecules and there is no in vivo or in vitro working examples or any evidence that the claimed chimeric molecules would have worked as intended for treatment or as pharmaceutical composition. The specification does not provide sufficient guidance as to how an artisan of skill would have made and used any claimed chimeric molecules for treatment and would have required extensive experimentation to make the claimed invention and use for the treatment and such experimentation would have been undue since neither the art nor the specification teaches treating any condition with the claimed chimeric molecules as discussed below and such experimentation was not routine in the art.

The specification provides the background information about the role of VEGFs in angiogenesis and that VEGFs can be used for producing angiogenic effects using a polypeptide angiogenic factor or a nucleic acid that encodes an angiogenic factor by administering polypeptide or nucleic acid in vivo (see page 2). The specification also raises the issue that despite the recent advances in topics related to angiogenesis, "there is no indication that the current methods would promote the level of angiogenesis required to overcome peripheral or cardiac ischemias." (see lines 7-16 on page 3). In pages 5-8, the specification discloses and discusses different angiogenic factors and their mechanism of action with emphasis on VEGF. In pages 19-47, the specification reviews the methodology used for targeting of molecules, gene therapy, vectors, protein therapy and other art recognized methods. In example 1, the specification teaches a method of expressing $VEGF_{167}$ in cell culture (in CHO cells). The specification, in examples 2-7 disclosed prophetic examples of constructing plasmids that can be used for expressing fusion proteins of VEGF or its splice variants (e.g. VEGF-b_{167}) in cells, and different methods of coupling VEGF with peptides for targeting. It is noted that the specification does not disclose whether the chimeric molecules disclosed in the specification were used in any in vitro or in vivo examples to determine the angiogenic properties of the claimed molecules.

First the issue is: is the specification enabling for making and using any chimeric molecule as recited in the claims? Except for teaching fusion proteins wherein an angiogenic factor protein is linked to a peptide, the specification does not provide any description for any other chimeric molecules. It is noted that an artisan would not have known how to make any chimeric molecule or what chimeric molecule in view of the lack of description of the chimeric molecules encompassed by the claimed invention. Courts have noted that patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. See Brenner v. Manson , 383 U.S. 519, 536, 148 USPQ 689, 696 (1966). Further, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling."

Next the issue is: is the specification enabling for the intended use that is, inducing angiogenesis when claimed chimeric molecules which comprises any angiogenic factor and any targeting molecule, are administered to a cell in vitro or to an animal in vivo? First, if the chimeric molecule is a fusion protein, (i) is the chimeric molecule taken up by the cell efficiently because depending on the nature of the targeting molecule, one may argue that the protein may not fold to its natural form and therefore may not be active. For example, the specification on page 47 discloses that VEGF-B167 is cell associated antiparallel dimer. The question is: would the fusion protein disclosed in examples 2-7 have formed the dimer that would have the activity of the native protein? The specification further discloses that to avoid sterical hinderance targeting peptide can be elongated by several additional amino acids on the C-terminal end. However, will the elongated peptide still recognize its receptor on the cells? Furthermore, claimed invention as presented may include the targeting peptide at the C-terminal or N-terminal end of the VEGF, however, the specification does not provide any guidance as to whether both the fusions will bind to the vascular endothelial cells. Next, the question is: does the chimeric molecule produce the biological activity because if the dimer formation of the VEGF is disrupted, VEGF may not be active. It is noted that when an expressed protein is to be used as a reagent in cell biology experiments, the authenticity of the protein's function, is very important. Claim 5 recites that the angiogenic factor is Ang2, endostatin or angiostatin, however, the specification does not provide any guidance as to whether the targeting molecule will be at the N-terminal or C-terminal end of the protein and whether after the N-terminal or C-terminal modification, the protein could fold and function as intended. While it is

agreed that an artisan could make a fusion protein, the real issue is: can an artisan use it for the intended utility and there is no evidence in the art or in the specification to indicate that the claimed molecules or compositions could be used for intended utility in view of the discussion above. The specification does not provide any guidance as to whether the claimed chimeric molecules would have bound to the vascular endothelium and whether they had the biological activity because the presence of the targeting molecule may have affected the dimer formation of VEGF or the structure or any other angiogenic factor.

Next issue is the bioavailability and half-life of the chimeric molecule when administered by different methods. For example, when administered by IP, IV or sub-cutaneous injections or injected into a particular tissue, what fraction of the administered chimeric molecule would have reached the targeted vascular endothelium because one would expect that different methods would result in different rates of elimination of the administered molecules. Again, the specification does not provide any guidance regarding the half life or bioavailability and stability of the chimeric molecule when administered by different routes and the chimeric molecules of the claimed invention may be eliminated before reaching the targeted cells.

Next the question is: will the chimeric molecule bind specifically to the vascular endothelium of all the tissues or even to all the different cells of a given tissue? Rajotte et al. (Rajotte D. et al. J Clin. Invest. 102:430-437, 1998) studied the molecular heterogeneity of the vascular endothelium using the phage display method and reported that there is not only heterogeneity of the endothelium between tissues, and even within a given tissue. For example, in lungs, ligands GFE-1 and GFE-2 stained mainly capillaries compared to larger vessels (page 436, col 1). This information is important for practicing the claimed invention because based on the method of the administration, the chimeric molecule may not even reach the target cells in an animal or the chimeric molecule expressed in transduced cells may not be disseminated to other tissues due to the lack or over-expression of the receptors of a given Logan at the site of administration. In fact, Rajotte et al, using phage displaying GFE-1 peptide observed that the phage in

circulation in a mouse rapidly bound to lung microvasculature but did not reach the corresponding receptor in kidney proximal tubules (see last paragraph in column 1 on page 11597 in Rajotte et al. J Biol. Chem. 11593-11598, 1999). Therefore, it is unpredictable whether claimed chimeric molecules would have reached the targeted site due to a particular method of administration. The specification does not provide any guidance as to whether the chimeric molecules disclosed in the specification would have reached to its targeted vascular endothelium, for example, to that of a particular organ or organs. In the absence of any in vivo or in vitro data, one cannot determine whether the chimeric molecules would have reached targeted vascular endothelium.

Furthermore, there is no evidence whether claimed fusion peptides would be delivered to endothelial cells of the cardiac vasculature or ischemic tissue because there is no evidence or working example to show that these molecules when administered to an animal in vivo or to cells in culture in vitro reached these cells and produced claimed effects. The specification on page 27, lines 2-13 discloses 4 different polypeptides and that the polypeptide GGGVFWA showed a 5 fold enrichment to normal vasculature, however, it is not clear how is this relevant to targeting to endothelium or cardiac vasculature and whether this peptide or any of the other peptides targeted the angiogenic factor to the claimed cells. For example, if a chimeric molecule administered by intravenous method reached the cardiac vasculature or ischemic tissue, what percent of the administered molecules would have reached the targeted vasculature and whether that level would have been sufficient to induce angiogenesis. The specification refers to a certain application filed by Campbell and Flores LLP and provides an Attorney docket number, however, there is no way for an artisan to know what is disclosed in this docket number application. Therefore, there is nothing on the record to show that these peptides would have targeted the fusion protein to endothelium. Regarding the peptide and protein therapy, it is noted that there is nothing on the record to indicate whether the chimeric protein or chimeric peptide when administered to an animal by different routes were taken up by the cells equally or was the uptake cell type dependent or what percent of the administered chimeric molecules would have

reached a target cell and whether such amount was sufficient to induce angiogenesis. Again, there is no evidence on record to show whether the claimed chimeric polypeptide or protein induced angiogenesis and to what level. Additionally, was there any interference in the biological activity of the angiogenic factors recited in the claimed invention due to fusion with targeting polypeptides? It is noted that the specification has not provided any evidence that the claimed molecules induced angiogenesis even in an in vitro system and therefore the claimed composition is not enabled for the intended use.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

11. Claims 1-4, 6, 7 and 28-29 rejected under 35 U.S.C. 102(e) as being anticipated by Hall et al (US 6,387,663, 5-14-02, effective filing date 7-31-98).

Hall et al discloses targeting pharmaceutical agents to injured tissues, wherein the targeting molecule is a fusion protein comprising VEGF-B165 and collagen binding domain (see figure 1). The patent also teaches that the collagen binding domain is of von Willenbrand factor, which targets platelet aggregates to vascular lesions. Accordingly, the claimed invention is anticipated by Hall et al.

12. Claims 1-4, 6, 7 and 28-29 rejected under 35 U.S.C. 102(b) as being anticipated by Olson et al (International Journal of Cancer 73:865-870, 1997).

Olson et al teaches targeting of tumor vasculature by providing a VEGF-toxin conjugate. The article teaches a fusion of VEGF-165 with truncated diphtheria toxin.

Therefore, the claimed invention is anticipated by Olson et al.

13. Claims 1-4, 6, 7 and 28-29 rejected under 35 U.S.C. 102(b) as being anticipated by Arora et al (Cancer Research 59:183-188, 1999; abstract only).

Arora et al teaches targeting of endothelial cells with a VEGF-toxin conjugate. The article teaches a fusion of VEGF-165 or VEGF-121 with truncated diphtheria toxin.

Therefore, the claimed invention is anticipated by Arora et al.

14. No claim is allowed.

When amending claims, applicants are advised to submit a clean version of each amended claim (without underlining and bracketing) according to § 1.121(c). For instructions, Applicants are referred to http://www.uspto.gov/web/offices/dcom/olia/aipa/index.htm.

Applicants are also requested to submit a copy of all the pending/under consideration claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The fax phone number for this Group is (703) 308-4242.

Ram R. Shukla, Ph.D.

RAM R. SHUKLA, PH.D
PATENT EXAMINER